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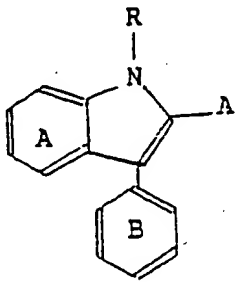
(54) Indole derivatives, their production and use.

(57) An agent for inhibiting bone resorption comprising an indole derivative of the formula (I):



(I)

wherein each ring of A and B is optionally substituted, R is a hydrogen atom, a lower alkyl group or an acyl group, and A is a hydroxymethyl group or an esterified or amidated carboxyl group; or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier, diluent or excipient.

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BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an inhibitor for bone resorption comprising indole derivatives as an active ingredient, said indole derivatives having activity for inhibiting bone resorption which is useful for treating osteoporosis.

2. Description of the Prior Arts

Osteoporosis is a morbidity or disease of bone showing any symptom or danger when bone reduction is more than some degree. The main symptoms are kyphosis or fractures of dorsolumbar bone, body of vertebra, neck of femur, distal extremity of radius, rib, proximal extremity of humerus or the like. Various causes of osteoporosis are given such as endocrinopathy or nutritional disorder. Conventional therapeutic agents for osteoporosis are estrogen, calcitonin, vitamin D and calcium.

The above-mentioned therapeutic agents, however, exhibit unsufficient effect, since said agents are limited on subjects to be administered and are uncertain on effect.

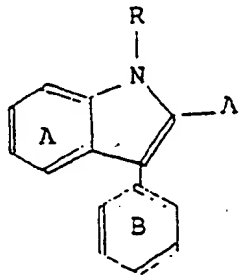
Some indole derivatives have been disclosed in Chem. Pharm. Bull., 19(2), pp.263-272 (1971); J. Org. Chem., Vol.37, No. 24, pp.3755-3770 (1972); J. Org. Chem., Vol. 38, No. 18, pp.3077-3084 (1973) and U.S. Patent No. 4,014,883. However, their activities for inhibiting bone resorption are not known.

SUMMARY OF THE INVENTION

As a result of earnest studies for developing more general agents directly acting on bone to inhibit bone resorption, the inventors of this invention have completed based upon the finding that indole derivatives of the formula (I) possess excellent activity for inhibiting bone resorption.

This invention relates to

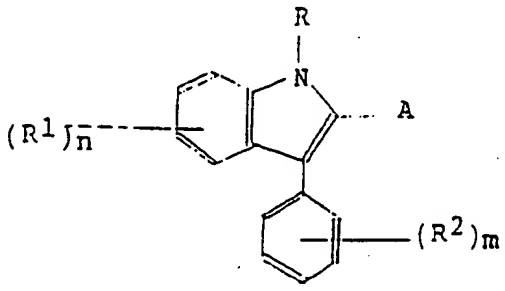
(1) an inhibitor for bone resorption comprising an indole derivative represented by the following formula (I):



(I)

wherein each ring of A and B is optionally substituted, R is a hydrogen atom, a lower alkyl group or an acyl group, and A is a hydroxymethyl group or an esterified or amidated carboxyl group;

(2) an indole derivative represented by the following formula (II):



(I')

wherein R^1 and R^2 each is, the same or different, an optionally substituted hydroxyl group or an optionally substituted alkyl group, or two of each of R^1 and R^2 may be a bivalent hydrocarbon residue or alkelenedioxy group to form a ring together with the ring to which they are attached, R is a hydrogen atom, a lower alkyl group or an acyl group, A is a hydroxymethyl group or an esterified or amidated carboxylic group and n and m each is an integer of two to four.

PREFERRED EMBODIMENT OF THE INVENTION

In the formula (I), when the ring A and/or ring B is substituted, examples of the substituents may be a halogen atom, an optionally substituted alkyl, aryl or alkenyl group or an optionally substituted hydroxyl group. The number of the substituents is one to four.

Examples of the halogen atoms are fluorine, chlorine, bromine or iodine, among which fluorine or chlorine is preferable.

The alkyl group in the optionally substituted alkyl group may be any one of straight-chain, branched-chain or cyclic alkyl group having one to ten carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, among which those having one to six carbon atoms are preferable.

Said alkyl group may have substituent(s) such as a halogen, nitro, amino (which may be substituted by an acyl, alkyl, iminomethyl, imino(aryl-substituted) methyl, amidino and/or amino), phosphoryl, alkoxyphosphoryl, sulfo, cyano, hydroxy, carboxy, hydrazino, imino, amidino, carbamoyl, aryl (which may be substituted by a halogen, alkyl, alkoxy, alkylamino, amino, carbamoyl, sulfo, alkylsulfonyl, cyano, hydroxy, carboxy, nitro, acyloxy, aralkyloxy, phosphoryl, alkoxyphosphoryl and/or sulfoxy), heterocycle (which may be substituted by nitro, oxo, aryl, alkenylene, halogenoalkyl, alkylsulfonyl, alkyl, alkoxy, alkylamino, amino, halogen, carbamoyl, hydroxy, cyano, carboxy, phosphoryl, alkoxyphosphoryl and/or sulfo) and the like.

The aryl group in the substituted or unsubstituted aryl group may be phenyl, naphthyl, biphenyl, anthryl, indenyl or the like.

The aryl group may have substituent(s) such as a halogen, nitro, cyano, amino (which may be substituted by an alkyl, alkenyl, cycloalkyl and/or aryl), phosphoryl, sulfo, hydroxy, sulfoxy, sulfamoyl, alkyl (which may be substituted by an amino, halogen, hydroxy, cyano and/or alkoxyphosphoryl), alkoxy, aralkyloxy, alkylsulfonamido, methylenedioxy, alkoxyphosphoryl, alkylsulfonyl, alkylsulphonylamino and the like. The aryl group may form a condensed ring together with a cycloalkyl (e.g., tetrahydronaphthyl, indanyl or acenaphthenyl).

The alkenyl group in the optionally substituted alkenyl group may be any straight-chain, branched-chain or cyclic group having two to ten carbon atoms, such as allyl, vinyl, crotyl, 2-penten-1-yl, 3-penten-1-yl, 2-hexen-1-yl, 3-hexen-1-yl, 2-cyclohexenyl, 2-cyclopentenyl, 2-methyl-2-propen-1-yl, 3-methyl-2-buten-1-yl or the like, among which these groups having two to six carbon atoms are preferable.

The alkenyl group may have substituent(s) such as an alkyl having one to six carbon atoms (said alkyl may have the same substituent(s) as those on the above-mentioned alkyl groups), halogen, nitro, amino (which may be substituted by an acyl, iminomethyl, amidino, alkyl and/or aryl), phosphoryl, sulfo, cyano, hydroxy, carboxy, alkyloxycarbonyl, carbamoyl, alkylthio, arylthio, alkylsulfinyl, arylsulfinyl, alkoxyphosphoryl, alkylsulfonyl, arylsulfonyl, sulfamoyl, aryl, acyl or the like. The above-mentioned alkenyl group or alkenylene group includes its isomers (E or Z form) with respect to the double bond.

Examples of the halogen atoms as the above-mentioned substituents are chlorine, bromine, fluorine or iodine.

Suitably, the alkyl groups as the substituent are those having one to ten carbon atoms, preferably having one to six carbon atoms, more preferably having one to four carbon atoms. Examples of those alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, isopentyl, n-hexyl, isohexyl, heptyl, octyl, nonyl, decyl or the like.

Preferably, the cycloalkyl groups as the above-mentioned substituent are those having three to six carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or the like.

Preferably, the alkoxy groups as the above-mentioned substituent are those having one to four carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy or the like.

Preferably, the aryl groups as the above-mentioned substituent are phenyl, naphthyl and the like.

Preferably, the heterocyclic groups as the above-mentioned substituent are pyridine, pyridazine, thiazole, oxazole, morpholine or the like.

Suitably, the acyl groups as the above-mentioned substituent are those having one to six carbon atoms, more preferably one to four carbon atoms, such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl,

isovaleryl, pivaloyl, hexanoyl or the like.

Preferably, the aralkyl groups as the above-mentioned substituent are benzyl, phenethyl, phenylpropyl and the like.

Preferable alkenyl or alkenylene groups as the above-mentioned substituents are methylene or the same ones as on the aforesaid alkenyl groups.

Examples of the substituted alkyl groups are trifluoromethyl, 2,2,2-trifluoroethyl, difluoromethyl, trichloromethyl, hydroxymethyl, 1- or 2-hydroxyethyl, 1- or 2-methoxyethyl, 1- or 2-ethoxyethyl, 2,2-dimethoxyethyl, 2,2-diethoxyethyl, 2-diethoxyphosphorylethyl or the like.

Examples of the substituted aryl groups include 4-chlorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, p-tolyl, 4-methoxyphenyl, 4-(N,N-dimethylamino)phenyl, 4-diethoxyphosphorylphenyl or the like.

Examples of the substituted alkenyl groups are 2,2-dichlorovinyl, 3-hydroxy-2-propen-1-yl, 2-methoxyvinyl and the like.

Examples of the optionally substituted hydroxyl groups are hydroxyl, or hydroxyl having an appropriate substituent, especially a protecting group for hydroxyl, such as an alkoxy, alkenyloxy, aralkyloxy, acyloxy or aryloxy. Preferably, said alkoxy groups are those having one to ten carbon atoms such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, n-pentoxy, isopentoxy, neopentoxy, hexyloxy, heptyloxy, nonyloxy, cyclobutoxy, cyclopentoxy or cyclohexyloxy). Preferably, said alkenyloxy groups are those having one to ten carbon atoms such as allyloxy, crotyloxy, 2-pentenyloxy, 3-hexenyloxy, 2-cyclopentenylmethoxy, 2-cyclohexenylmethoxy or the like. Preferably, said aralkyloxy groups are phenyl-C_{1-4} alkyloxy (e.g., benzyloxy or phenethyloxy). Preferably, said acyloxy groups are alkanoyloxy (e.g., acetyloxy, propionyloxy, n-butyryloxy or isobutyryloxy) or the like. Examples of said aryloxy groups are phenoxy, 4-chlorophenoxy or the like.

Each of the alkyl, alkenyl, acyl and aryl groups in the alkyloxy, alkenyloxy, aralkyloxy, acyloxy and aryloxy groups may have substituent(s) such as a halogen (e.g., fluorine, chlorine, bromine or iodine), hydroxyl, alkoxy having one to six carbon atoms(e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, n-pentyloxy or n-hexyloxy) or the like. The number of the substituents is preferably one to three.

Examples of said alkyloxy, alkenyloxy, aralkyloxy, acyloxy and aryloxy groups having substituent(s) are trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, 2-methoxyethoxy, 4-chlorobenzyloxy, 2-(3,4-dimethoxyphenyl)ethoxy or the like.

In the case where the ring A and/or ring B are substituted, their substituent is preferably the optionally substituted hydroxyl group.

When there are two or more substituents on the ring A and/or ring B, these substituents may be a bivalent hydrocarbon residue or alkylenedioxy group to form a ring together with the ring A or B. For example, two substituents bond together to form a ring represented by the formula of $-(CH_2)_l-$, $-(CH=CH)_k-$ or $-O(CH_2)_pO-$ (in which l, k and p each represents an integer.) This ring may form a 5-, 6- or 7-membered ring together with the adjacent two carbon atoms in the ring A or B.

Examples of the lower alkyl groups represented by R in the formula (I) are straight-chain, branched-chain or cyclic groups having one to six carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

Examples of the acyl groups are those produced by combining the above-mentioned alkyl groups (preferably having one to six carbon atoms) with a carbonyl group.

Preferable groups for R are hydrogen atom or lower alkyl groups having one to three carbon atoms.

Examples of the ester residues in the esterified carboxyl group represented by A in the formulas (I) and (I') are the lower alkyl groups in the explanation of R or aralkyl groups having seven to fifteen carbon atoms such as benzyl, phenethyl, phenylpropyl, benzhydryl or the like. The aralkyl group may be substituted by one to three of a halogen or alkoxy group having one to four carbon atoms.

Preferable amidated carboxyl groups are those formed by combining an amino group which may be substituted by an optionally substituted hydrocarbon residue with a carbonyl group. Examples of the optionally substituted hydrocarbon residues are optionally substituted alkyl, aryl, alkenyl or heterocyclic groups. The explanations of the optionally substituted alkyl, aryl and alkenyl groups are the same as those for the ring A and/or ring B in the formula (I).

Examples of the optionally substituted heterocyclic groups are 5-7 membered heterocyclic groups having one sulfur, nitrogen or oxygen atom, 5-6 membered heterocyclic groups having two to four nitrogen atoms or 5-6 membered heterocyclic groups having one or two nitrogen atoms and one sulfur or oxygen atom. These heterocyclic groups may be condensed with a 6-membered ring having two or less nitrogen atoms, a 5-membered ring having one sulfur atom or a benzene ring.

Examples of the heterocyclic groups are 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl,

pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrido[2,3-d] pyrimidyl, benzopyranyl, 1,8-naphthyridyl, 1,5-naphthyridyl, 1,6-naphthyridyl, 1,7-naphthyridyl, quinolyl, thieno[2,3-b]pyridyl, tetrazolyl, thiadiazolyl, oxadiazolyl, triazinyl, triazolyl, thienyl, pyrrolyl, pyrrolinyl, furyl, pyrrolidinyl, benzothienyl, indolyl, imidazolidinyl, piperidyl, piperidino, piperazinyl, morpholinyl, morpholino and the like.

Said heterocyclic groups may have substituent(s) such as an amino (which may be substituted by an acyl, halogen, acyl, phenyl and/or alkyl), halogen, nitro, sulfo, cyano, hydroxy, carboxy, oxo, thioxo, alkyl having one to 10 carbon atoms (which may be substituted by an aryl, halogen, amino, hydroxy, carboxy, alkoxy, alkylsulfonyl and/or dialkylamino), cycloalkyl, alkoxy (which may be substituted by a halogen and/or hydroxy), acyl having one to four carbon atoms, aryl (which may be substituted by a halogen, nitro, alkyl, alkoxy, amino, sulfo, hydroxy and/or cyano) or oxo or the like.

Examples of the substituted heterocyclic groups are 5-chloro-2-pyridyl, 3-methoxy-2-pyridyl, 5-methyl-2-benzothiazolyl, 5-methyl-4-phenyl-2-thiazolyl, 3-phenyl-5-isoxazolyl, 4-(4-chlorophenyl)-5-methyl-2-oxazolyl, 3-phenyl-1,2,4-thiadiazole-5-yl, 5-methyl-1,3,4-thiadiazole-2-yl, 5-acetylamino-2-pyrimidyl, 3-methyl-2-thienyl, 4,5-dimethyl-2-furanyl, 4-methyl-2-morpholinyl or the like.

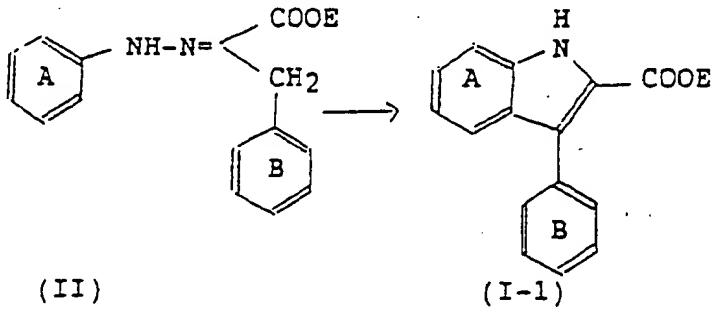
Preferably, optionally substituted alkyl groups and hydroxyl groups represented by R^1 and R^2 in the formula (I') are the optionally substituted alkyl and optionally substituted hydroxyl groups exemplified as the substituent of the ring A and ring B in the formula (I). The explanations of each substituent for the above groups are the same as those explained in the formula (I).

When there are two or more substituents on each benzene ring in the formula (I'), two substituents on the same benzene ring may be a bivalent hydrocarbon residue or alkelenedioxy group to form a ring together with the benzene ring to which the substituents are attached. Their examples are as explained above.

The explanations of the substituents represented by R and A in the formula (I') are the same as those explained in the formula (I).

The object compounds of the present invention can be prepared, for example, by any of the following methods.

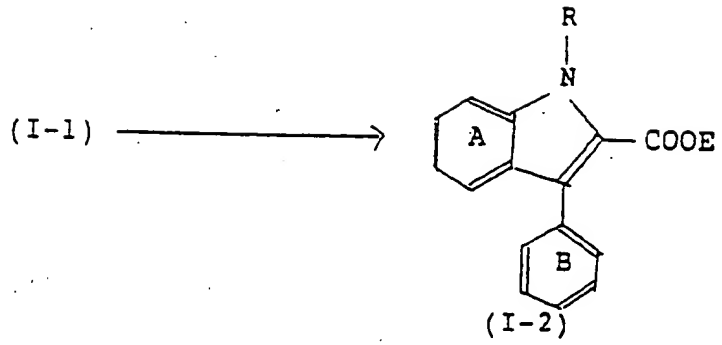
Method A



(II) (I-1)

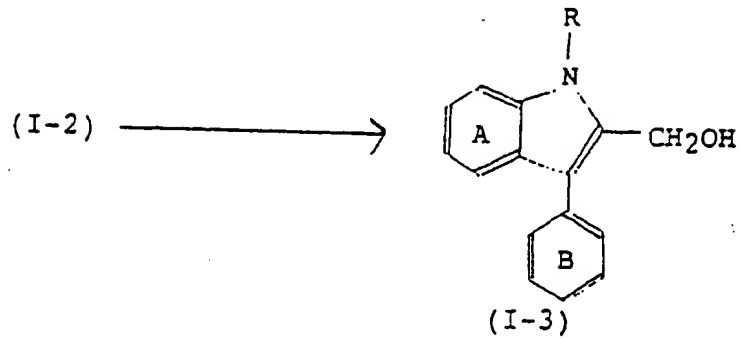
wherein E has the same meaning as the ester residue in the explanation of the substituent A and the ring A and ring B have the same meanings as defined above.

Method B



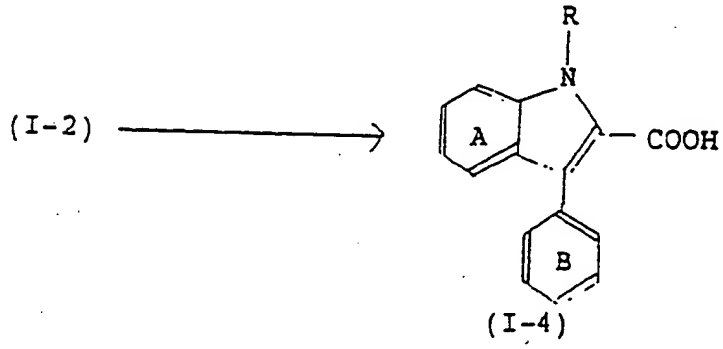
wherein the ring A, ring B, R and E have the same meanings as defined above.

Method C



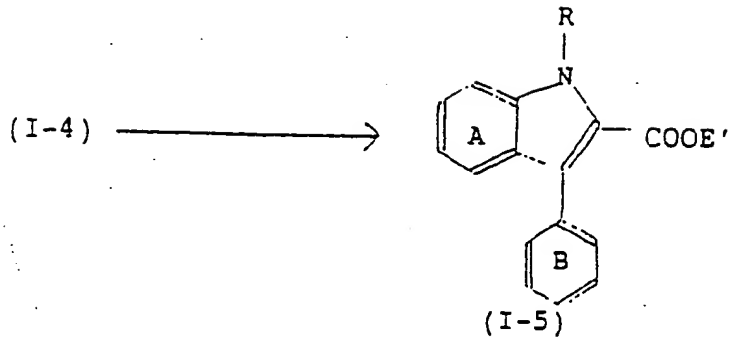
wherein the ring A, ring B and R have the same meanings as defined above.

Method D



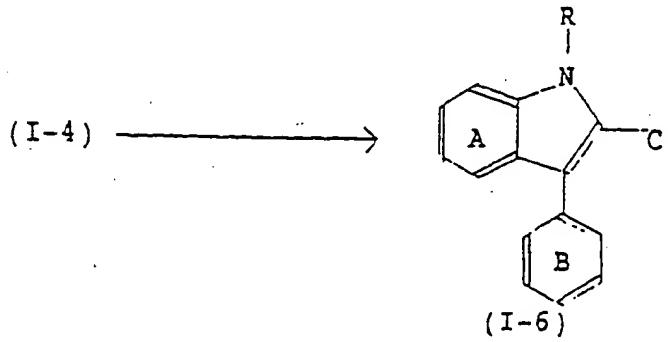
wherein the ring A, ring B and R have the same meanings as defined above.

Method E



wherein E' has the same meanings as the ester residues in the explanation of the substituents represented by A and a ring A, ring B and R have the same meanings as defined above.

Method F



wherein C has the same meaning as the amidated carboxyl group in the explanation of the substituent A and the ring A, ring B and R have the same meanings as defined above.

Method G

When the ring A and/or ring B are substituted with a substituted hydroxyl group in the compound (I), a phenol derivative can be prepared by eliminating said substituent of hydroxyl group.

Method H

When the ring A and/or ring B are substituted with a hydroxyl group in the compound (I), a hydroxyl group substituted by alkyl, aralkyl or acyl can be prepared from the above phenolic derivative.

Each method will be explained hereinbelow.

Method A

The compound (I-1) can be prepared by heating the compound (II) in an appropriate solvent or without any solvent in the presence of an appropriate acid.

The cyclization from the compound (II) to the compound (I-1) in this method can be carried out by the same manner as the conventional Fisher Indole Synthesis. The synthesis is conducted by any known method, for example, W. Sumpter, F. Miller, The Chemistry of Heterocyclic Compounds, 8, Heterocyclic Compounds with Indole and Carbazole Systems [Interscience Publishers, Inc. New York, (1954)]; W. Houlihan, 25, pp.232 [Wiley-Interscience, (1972)]; Shinjikken Kagakukoza 14, Synthesis and Reaction of Organic Compound (IV) [Chemical Society of Japan, Maruzen, (1978)]; and Daiyukikagaku 14, Heterocyclic Compounds 1, pp.342 [Asakura Shoten, (1959)]. For example, the synthesis is carried out in a solvent such

as an alcohol (e.g., ethanol, methanol, propanol, isopropanol or the like) in the presence of hydrochloric acid, sulfuric acid, acetic acid, formic acid, phosphoric anhydride or Lewis acid (e.g., zinc chloride). The acid is used preferably in an amount of from about 0.5 to 10 mols to one mol of the compound (II). The reaction temperature is usually from about 10°C to 200°C, preferably from about 30°C to 150°C. The reaction time is about 0.5 to 100 hours, preferably about 1 to 30 hours. Acetic acid can be used as a solvent when it is used as an acid catalyst. The compound (II), which is the starting material in this method, can be prepared by known Japp-Klingemann reaction disclosed in The Chemistry of Heterocyclic Compounds, 8, Heterocyclic Compounds with Indole and Carbazole Systems by W. Sumpter, F. Miller [Interscience Publishers, Inc., New York (1954)].

Method B

The compound (I-2) can be prepared by reacting the compound (I-1) with a compound represented by the formula R-X [in which X is a leaving group such as a halogen (e.g., chlorine, bromine or iodine) or sulfonyloxy (e.g., mesyloxy, tosyloxy or benzenesulfonyloxy) and R has the same meaning as defined above] in the presence of a base (e.g., sodium hydride, potassium hydride, sodium amide, triethylamine, N-methylmorpholine, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate or the like). This reaction is carried out in a suitable solvent such as tetrahydrofuran, dioxane, ether, toluene, xylene, benzene, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane, N,N-dimethylformamide, dimethylsulfoxide or the like) at a temperature of about -20°C to 100°C, preferably about -10°C to 50°C. The compound (R-X) is preferably used in an excess amount to the compound (I-1).

Method C

This reaction can be conducted by a known reduction method, for example, a method disclosed in Shinjikken Kagakukoza 15, Oxidation and Reduction [II] (Maruzen, 1977), a reduction with a metal and a metal salt, reduction with a metal hydride compound, reduction with a metal hydride complex, reduction by a hydrogen tranfer reaction or reduction by a catalytic hydrogenation and so on.

Method D

The compound (I-4) can be prepared by hydrolyzing the compounds (I-1) or (I-2) prepared in Method A or Method B. The hydrolysis can be carried out by a known method in a solvent in the presence of an acid such as hydrochloric acid, sulfuric acid, acetic acid, hydrobromic acid or the like or a base such as potassium carbonate, sodium carbonate, sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium hydroxide, potassium hydroxide, lithium hydroxide or the like. Suitable solvents to be used are mixtures of water and organic solvents such as alcohols (e.g., methanol or ethanol), ether (e.g., tetrahydrofuran or dioxane), N,N-dimethylformamide, dimethylsulfoxide, acetone and the like. The acid or base is preferably used in an excess amount (base: 1.2 to 6 equivalents; acid: 2 to 50 equivalents) to the compound (I-1) or (I-2). The reaction is carried out at about -20°C to 150°C, preferably about -10°C to 100°C.

Method E

The compound (I-5) can be prepared by esterifying the carboxylic acid derivative (I-4). This esterification can be conducted by any known method, for example, a method for directly reacting the compound (I-4) with an alkyl halide in the presence of a base or a method for reacting an alcohol with a reactive derivative of the compound (I-4) such as acid anhydride, acid halide (e.g., acid chloride or acid bromide), imidazolide or mixed anhydride (e.g., anhydride with methyl carbonate, anhydride with ethyl carbonate, anhydride with isobutyl carbonate or the like).

Method F

The compound (I-6) can be prepared by amidating the carboxylic acid derivative (I-4). This reaction can be conducted by any known method, for example, a method for directly condensing the compound (I-4) and an amine derivative in the presence of dicyclohexyl carbodiimide or the like or a method for reacting an amine derivative with a reactive derivative of the compound (I-4), such as acid anhydride, acid halide (e.g., acid chloride or acid bromide), imidazolide or mixed anhydride (e.g., anhydride with methyl carbonate,

anhydride with ethyl carbonate, anhydride with isobutyl carbonate or the like). The most convenient method is the one using the acid halide or mixed anhydride of the compound (I-4). In the case of using the acid halide, the reaction is carried out in a solvent (e.g., chloroform, dichloromethane, ethyl acetate, tetrahydrofuran, water or mixture thereof) in the presence of a base (e.g., triethylamine, N-methylmorpholine, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate or potassium carbonate) at about -10 °C to 50 °C. The amine derivative is used in an amount of about 1 to 1.2 mols to the compound (I-4). In the case of using the mixed anhydride, the compound (I-4) is preferably reacted with a chlorocarbonic ester (e.g., methyl chlorocarbonate, ethyl chlorocarbonate or isobutyl chlorocarbonate) in the presence of a base (e.g., triethylamine, N-methylmorpholine, sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate or potassium carbonate) in a suitable solvent (e.g., chloroform, dichloromethane, ethyl acetate, tetrahydrofuran, water or mixture thereof) at about -10 °C to 30 °C. The amount of the amine derivative to be used is about 1 to 1.2 mols to the compound (I-4).

Method G

The compound (I) in which the ring A and/or B have a substituted hydroxyl group can eliminate its substituent of hydroxyl group to afford a phenol derivative. The conversion of the alkyloxy or aralkyloxy derivative to the phenol derivative can be preferably conducted by use of boron tribromide or boron trichloride. This reaction is carried out in an inert solvent such as carbon tetrachloride, chloroform, dichloromethane, 1,2-dichloroethane, 1,1,2,2-tetrachloroethane or the like at about -50 °C to 40 °C, preferably about -20 °C to 30 °C. Boron tribromide or boron trichloride is used in an excess amount to the compound (I). The conversion of the acyloxy derivatives to the phenol derivatives is conducted by the same manner as in Method D.

Method H

The hydroxyl group substituted by an alkyl, aralkyl or acyl can be prepared from the compound (I) in which the substituent on the ring A and/or ring B is a hydroxyl group.

The alkylation or aralkylation of the hydroxyl group can be carried out by the same manner as in Method B or analogous ones thereto. The acylation can be conducted by any known methods. Generally, the acylation is carried out by reacting, in an anhydrous organic solvent, the compound (I) with an acylating agent which can introduce the above-mentioned acyl group, such as acid halide, acid anhydride, activated ester of carboxylic acid or the like. The reaction can be carried out in the presence of an appropriate organic or inorganic base at about 0 °C to 70 °C, preferably about 20 °C to 50 °C for about 0.5 to 48 hours, preferably about 1 to 20 hours.

A pharmaceutically acceptable acid addition salt of the compound (I) can easily be prepared by reacting the compound (I) with an inorganic acid such as hydrochloric acid, sulfuric acid, hydrobromic acid or phosphoric acid or an organic acid such as maleic acid, fumaric acid, tartaric acid, citric acid, oxalic acid or benzoic acid by known methods.

Further, a pharmaceutically acceptable salt with an alkali metal such as potassium or sodium can be prepared from the compound (I) having in its molecule an acid group such as carboxylic acid.

A method for preparing the compound (I) will hereinbelow be explained with reference to Reference Examples and Examples, by which this invention shall not be limited.

Reference Example 1

A solution of sodium nitrite (0.414 g) in water (2.0 ml) was dropwise added to a solution of 3,4-xylidine (0.61 g) in concentrated hydrochloric acid (1.5 ml) at a temperature of 0 °C, followed by stirring for 30 minutes at 0 °C. To the mixture were added sodium acetate (1.23 g) and methyl 2-(3,4-dimethoxybenzyl)-acetoacetate (1.33 g). After stirring for an hour at room temperature, the reaction mixture was poured into water and extracted with ethyl ether. The ethereal layer was washed with a saturated sodium hydrogencarbonate aqueous solution and water, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in methanol (20 ml), to which 1N-KOH methanolic solution (5 ml) was dropwise added at 0 °C. After stirring for an hour at 0 °C, the resultant mixture was neutralized with acetic acid and poured into water. The precipitate was collected by filtration and recrystallized from acetone-methanol to give methyl 3-(3,4-dimethoxyphenyl)-2-(3,4-dimethylphenylhydrazino)propionate (1.25 g, 70%) as pale red prisms.
mp: 148 - 150 °C

Elementary Analysis for $C_{20}H_{24}N_2O_4$

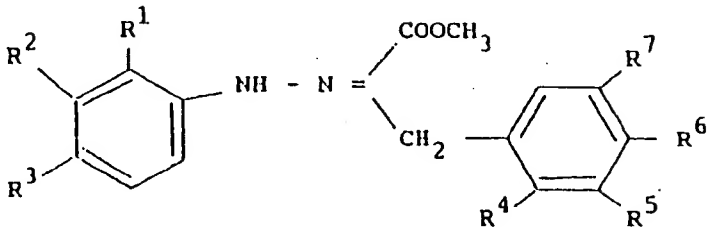
Calc.: C, 67.40; H, 6.79; N, 7.86

Found: C, 67.62; H, 6.87; N, 7.82

Reference Examples 2 - 41

Compounds listed in Table 1 were obtained by the same manner as in Reference Example 1.

Table 1



No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
2	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	78	142-144	methanol
3	H	CH_3O	CH_3O	H	H	CH_3O	H	64	101-102	ether*
4	H	CH_3O	CH_3O	H	$-OCH_2O-$		H	73	97- 99	ether
5	H	CH_3O	CH_3O	H	H	CH_3	H	60	109-110	ether
6	H	CH_3O	CH_3O	H	H	H	H	66	107-108	ether
7	H	CH_3O	CH_3O	H	CH_3	CH_3	H	50	117-118	methanol
8	H	CH_3O	CH_3O	H	Cl	Cl	H	58	92- 93	isopropyl ether
9	H	CH_3O	CH_3O	H	H	Cl	H	66	123-124	methanol

* ethyl ether

Table 1 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
10	H	CH_3O	CH_3O	CH_3O	H	H	CH_3O	70	103-104	isopropyl ether
11	H	CH_3O	CH_3O	H	CH_3O	H	CH_3O	50	118-119	ether
12	H	CH_3O	CH_3O	H	C_2H_5O	C_2H_5O	H	65	98- 99	methanol - water
13	H	CH_3O	CH_3O	H	H	C_2H_5O	H	57	116-117	ether
14	H	$-OCH_2O-$		H	CH_3O	CH_3O	H	58	174-175	methanol
15	H	$-O(CH_2)_2O-$		H	CH_3O	CH_3O	H	76	181-183	chloroform - acetone
16	H	H	CH_3O	H	CH_3O	CH_3O	H	76	144-145	acetone - methanol
17	H	H	CH_3	H	CH_3O	CH_3O	H	70	175-177	acetone - methanol
18	CH_3	H	CH_3	H	CH_3O	CH_3O	H	78	157-158	acetone - methanol

Table 1 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
19	H	H	H	H	CH_3O	CH_3O	H	66	155-157	acetone - methanol
20	H	H	Cl	H	CH_3O	CH_3O	H	30	204-206	acetone - methanol
21	H	Cl	CH_3	H	CH_3O	CH_3O	H	21	149-150	methanol
22	H	$-(CH_2)_3-$		H	CH_3O	CH_3O	H	75	149-150	acetone - methanol
23	$-(CH_2)_4-$		H	H	CH_3O	CH_3O	H	46	158-159	acetone - methanol
24	H	$-O(CH_2)_2O-$		H	H	CH_3O	H	74	125-127	ether
25	H	CH_3	CH_3	H	H	CH_3O	H	76	115-116	methanol
26	H	H	CH_3O	H	CH_3	CH_3	H	71	93- 94	methanol
27	H	H	CH_3O	H	H	CH_3O	H	89	oil [1]	-
28	H	H	CH_3O	H	H	C_2H_5O	H	84	oil [2]	-

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Table 1 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
29	H	H	H	H	H	H	H	58	88- 89	iscpropyl ether
30	H	CH_3	CH_3	H	H	CH_3	H	70	99-100	isopropyl ether
31	H	H	CH_3	H	H	H	H	97	oil [3]	-
32	H	H	CH_3	H	CH_3	CH_3	H	52	110-111	methanol - water
33	H	H	CH_3	H	H	Cl	H	93	oil [4]	-
34	H	H	CH_3	H	Cl	Cl	H	70	122-123	acetone - methanol
35	H	H	CH_3	H	H	CH_3	H	57	89- 90	isopropyl ether

Table 1 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
36	H	CH_3O	CH_3O	H	CH_3O	CH_3O	CH_3O	42	132-133	acetone-methanol
37	H	$-O(CH_2)_2O-$		H	CH_3O	CH_3O	CH_3O	37	137-138	methanol-dichloromethane
38	H	$-OCH_2O-$		H	C_2H_5O	C_2H_5O	H	28	128-129	ethyl acetate-hexane
39	H	$-O(CH_2)_2O-$		CH_3O	H	CH_3O	CH_3O	74	132-133	ethyl acetate-hexane
40	H	CH_3O	CH_3O	CH_3O	H	CH_3O	CH_3O	73	136-137	ethyl acetate-hexane
41	H	$-OCH_2O$		CH_3O	H	CH_3O	CH_3O	46	136-137	ethyl acetate-hexane

Note 1) to 4): crude oil

Example 1

A mixture of methyl 2-(3,4-dimethoxyphenylhydrazino)-3-(3,4-dimethylphenyl)propionate (0.8 g), concentrated sulfuric acid (1 ml) and methanol (25 ml) was refluxed for 4 hours. The reaction mixture was

poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from ethyl ether to give methyl 5,6-dimethoxy-3-(3,4-dimethylphenyl)indole-2-carboxylate (0.457 g, 60%) as colorless prisms.

mp: 185 - 186 °C

Elementary Analysis for $C_{20}H_{21}NO_4$

Calc.: C, 70.78; H, 6.24; N, 4.13

Found: C, 70.83; H, 6.32; N, 4.10

Examples 2 - 41

Compounds listed in Table 2 were obtained by the same manner as in Example 1.

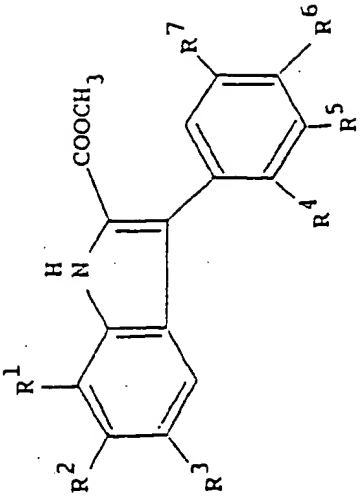


Table 2

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
2	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	68	164-166	acetone - methanol
3	H	CH_3O	CH_3O	H	H	CH_3O	H	73	162-163	acetone - methanol
4	H	CH_3O	CH_3O	H	$-OCH_2O-$		H	69	214-216	acetone - methanol
5	H	CH_3O	CH_3O	H	H	CH_3	H	66	174-175	ether
6	H	CH_3O	CH_3O	H	H	H	H	69	151-152	ether

Table 2 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
7	H	CH_3O	CH_3O	H	Cl	Cl	H	51	178-179	ether
8	H	CH_3O	CH_3O	H	H	Cl	H	58	193-194	ether
9	H	CH_3O	CH_3O	CH_3O	H	H	CH_3O	58	195-196	methanol
10	H	CH_3O	CH_3O	H	CH_3O	H	CH_3O	61	160-161	methanol
11	H	CH_3O	CH_3O	H	C_2H_5O	C_2H_5O	H	41	149-150	methanol
12	H	CH_3O	CH_3O	H	H	C_2H_5O	H	73	160-161	methanol
13	H	$-OCH_2O-$		H	CH_3O	CH_3O	H	65	245-247	acetone
14	H	$-O(CH_2)_2O-$		H	CH_3O	CH_3O	H	46	235-237	acetone - methanol
15	H	CH_3	CH_3	H	CH_3O	CH_3O	H	56	223-225	ethyl acetate
16	H	H	CH_3O	H	CH_3O	CH_3O	H	41	159-160	ether
17	H	H	CH_3	H	CH_3O	CH_3O	H	46	158-160	ether
18	CH_3	H	CH_3	H	CH_3O	CH_3O	H	35	174-175	ether

Table 2 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
19	H	H	H	H	CH_3O	CH_3O	H	30	179-180	ether
20	H	H	Cl	H	CH_3O	CH_3O	H	7	150-151	ether - hexane
21	H	Cl	CH_3	H	CH_3O	CH_3O	H	16	212-213	ether
22	H	$-(CH_2)_3-$		H	CH_3O	CH_3O	H	46	185-186	methanol
23	$-(CH_2)_4-$		H	H	CH_3O	CH_3O	H	55	225-227	acetone
24	H	$-O(CH_2)_2O-$		H	H	CH_3O	H	58	200-202	acetone - methanol
25	H	CH_3	CH_3	H	H	CH_3O	H	56	214-215	ethyl acetate
26	H	H	CH_3O	H	CH_3	CH_3	H	51	181-182	ether
27	H	H	CH_3O	H	H	CH_3O	H	28 1)	152-153	ether
28	H	H	CH_3O	H	H	C_2H_5O	H	12 2)	161-162	isopropyl ether

Table 2 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
29	H	H	H	H	H	H	H	79	138-139	methanol
30	H	CH_3	CH_3	H	H	CH_3	H	65	203-204	acetone - methanol
31	H	H	CH_3	H	H	H	H	59 [3)]	171-172	acetone - methanol
32	H	H	CH_3	H	CH_3	CH_3	H	81	163-164	methanol
33	H	H	CH_3	H	H	Cl	H	58 [4)]	188-189	acetone - methanol
34	H	H	CH_3	H	Cl	Cl	H	64	172-173	acetone - methanol
35	H	H	CH_3	H	H	CH_3	H	82	167-168	methanol

Table 2 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield (%)	MP(°C)	Solvent for recrystallization
36	H	CH_3O	CH_3O	H	CH_3O	CH_3O	CH_3O	24	179-180	methanol
37	H	$-O(CH_2)_2O-$		H	CH_3O	CH_3O	CH_3O	74	204-205	methanol-chloroform
38	H	$-OCH_2O-$		H	C_2H_5O	C_2H_5O	H	44	208-209	ethyl acetate-hexane
39	H	$-O(CH_2)_2O-$		CH_3O	H	CH_3O	CH_3O	34	190-191	ethyl acetate-hexane
40	H	CH_3O	CH_3O	CH_3O	H	CH_3O	CH_3O	34	104-105	ethyl acetate-hexane
41	H	$-OCH_2O-$		CH_3O	H	CH_3O	CH_3O	30	218-219	ethyl acetate-hexane

1) Yield from Reference Example 27
2) Yield from Reference Example 28
3) Yield from Reference Example 31
4) Yield from Reference Example 33

Example 42

To a solution of methyl 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylate (7.5 g) in N,N-dimethylformamide (100 ml) was added oily sodium hydride (60%, 1.6 g) and the mixture was stirred for 30

minutes at room temperature. After dropwise addition of ethyl iodide (4.8 ml), the reaction mixture was further stirred for 2 hours at room temperature, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from ethyl ether to give methyl 1-ethyl-5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylate (6.38 g, 77%) as pale red prisms.
mp: 191 - 192 °C

Elementary Analysis for $C_{22}H_{25}NO_6$

Calc.: C, 66.15; H, 6.31; N, 3.51

Found: C, 66.14; H, 6.43; N, 3.35

Examples 43 - 75

Compounds listed in Table 3 were obtained by the same manner as in Example 42.

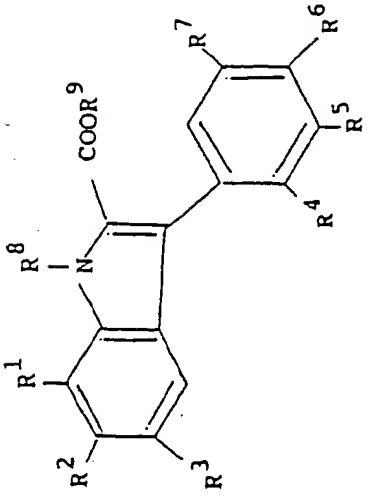


Table 3

No. of Example	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Yield (%)	MP(°C)	Solvent for recrystallization
43	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	CH_3	CH_3	93	206-208	acetone
44	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$n\text{-}C_3H_7$	CH_3	74	131-132	ether
45	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$(CH_3)_2CH$	CH_3	90	147-149	methanol
46	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$n\text{-}C_4H_9$	CH_3	74	118-119	ether
47	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$n\text{-}C_5H_{11}$	CH_3	73	116-117	ether
48	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$COOC_2H_5$	CH_3	82	148-150	acetone
49	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$CH_2COOC_2H_5$	CH_3	91	197-199	ethyl acetate

Table 3 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Yield (%)	MP(°C)	Solvent for recrystallization
50	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$COOCH_2Ph$	CH_3	84	121-122	ether
51	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$COCH_3$	CH_3	64	158-159	acetone
52	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	COC_2H_5	CH_3	49	158-160	ether
53	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	$COCH=CHCH_3$	CH_3	12	152-154	ether
54	H	CH_3O	CH_3O	H	CH_3O	CH_3O	H	C_2H_5	$(CH_3)_3C$	87	128-129	ether
55	H	$-O(CH_2)_2O-$		H	CH_3O	CH_3O	H	C_2H_5	CH_3	88	224-225	chloroform-methanol
56	H	$-OCH_2O-$		H	CH_3O	CH_3O	H	C_2H_5	CH_3	77	203-204	chloroform-acetone
57	H	CH_3O	CH_3O	H	CH_3O	CH_3O	CH_3O	C_2H_5	CH_3	67	142-143	methanol
58	H	$-O(CH_2)_2O-$		H	CH_3O	CH_3O	CH_3O	CH_3	CH_3	32	160-161	methanol - dichloromethane
59	H	$-O(CH_2)_2O-$		H	CH_3O	CH_3O	CH_3O	C_2H_5	CH_3	60	161-162	methanol - dichloromethane
60	H	$-O(CH_2)_2O-$		H	CH_3O	CH_3O	CH_3O	$(CH_3)_2CH$	CH_3	18	190-191	methanol - dichloromethane

Table 3 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Yield (%)	MP(°C)	Solvent for recrystallization
61	H	$-O(CH_2)_2O-$		H	C_2H_5O	C_2H_5O	H	CH_3	CH_3	81	174-175	ethyl acetate-hexane
62	H	$-O(CH_2)_2O-$		H	C_2H_5O	C_2H_5O	H	C_2H_5	CH_3	60	181-182	ethyl acetate-hexane
63	H	$-O(CH_2)_2O-$		H	C_2H_5O	C_2H_5O	H	$(CH_3)_2CH$	CH_3	53	155-156	ethyl acetate-hexane
64	H	$-OCH_2O-$		H	C_2H_5O	C_2H_5O	H	CH_3	CH_3	89	156-157	ethyl acetate-hexane
65	H	$-OCH_2O-$		H	C_2H_5O	C_2H_5O	H	C_2H_5	CH_3	90	178-179	ethyl acetate-hexane
66	H	$-OCH_2O-$		H	C_2H_5O	C_2H_5O	H	$(CH_3)_2CH$	CH_3	11	144-145	ethyl acetate-hexane
67	H	$-O(CH_2)_2O-$		CH_3O	H	CH_3O	CH_3O	CH_3	CH_3	73	187-188	ethyl acetate-hexane
68	H	$-O(CH_2)_2O-$		CH_3O	H	CH_3O	CH_3O	C_2H_5	CH_3	59	191-192	ethyl acetate-hexane

Table 3 (continued)

No. of Examples	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Yield (%)	MP(°C)	Solvent for recrystalli-zation
69	H	$-O(CH_2)_2O-$		CH_3O	H	CH_3O	CH_3O	$(CH_3)_2CH$	CH_3	13	178-179	ethyl acetate-hexane
70	H	CH_3O	CH_3O	CH_3O	H	CH_3O	CH_3O	CH_3	CH_3	60	158-159	ethyl acetate-hexane
71	H	CH_3O	CH_3O	CH_3O	H	CH_3O	CH_3O	C_2H_5	CH_3	60	135-136	ethyl acetate-hexane
72	H	CH_3O	CH_3O	CH_3O	H	CH_3O	CH_3O	$(CH_3)_2CH$	CH_3	33	157-158	ethyl acetate-hexane
73	H	$-OCH_2O-$		CH_3O	H	CH_3O	CH_3O	CH_3	CH_3	92	192-193	ethyl acetate-hexane
74	H	$-OCH_2O-$		CH_3O	H	CH_3O	CH_3O	C_2H_5	CH_3	84	153-154	ethyl acetate-hexane
75	H	$-OCH_2O-$		CH_3O	H	CH_3O	CH_3O	$(CH_3)_2CH$	CH_3	42	179-180	ethyl acetate-hexane

Example 76

A solution of methyl 5,6-dimethoxy-3-(4-methoxyphenyl)indole-2-carboxylate (0.25 g) in tetrahydrofuran (10 ml) was dropwise added to a suspension of lithium aluminum hydride ($LiAlH_4$) (56 mg) in

tetrahydrofuran (10 ml) at room temperature, followed by stirring for 2 hours at room temperature. After adding water, the mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from acetone to give 2-hydroxymethyl-5,6-dimethoxy-3-(4-methoxyphenyl)-indole (0.145 g, 63%) as colorless prisms.
mp: 169 - 170 °C

Elementary Analysis for $C_{18}H_{19}NO_4$

Calc.: C, 68.99; H, 6.11; N, 4.47

Found: C, 68.93; H, 6.21; N, 4.39

Examples 77 - 80

Compounds listed in Table 4 were obtained by the same manner as in Example 76.

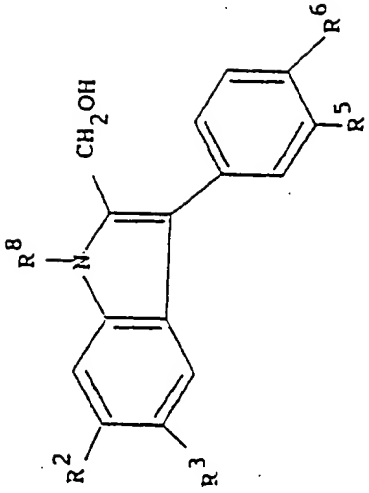


Table 4

No. of Examples	R^2	R^3	R^5	R^6	R^8	Yield (%)	MP(°C)	Solvent for recrystallization
77	CH_3O	CH_3O	CH_3O	CH_3O	H	69	165 - 167	ether
78	$-O(CH_2)_2O-$		CH_3O	CH_3O	H	68	201 - 202	acetone - isopropylether
79	CH_3O	CH_3O	CH_3O	CH_3O	C_2H_5	83	182 - 183	acetone
80	CH_3O	CH_3O	CH_3O	CH_3O	$(CH_3)_2CH$	70	140 - 141	ether

Example 81

A mixture of methyl 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylate (0.54 g), 2N-NaOH (10 ml) and methanol (25 ml) was refluxed for 3 hours under stirring. The reaction mixture was poured into

water, acidified with 6N-HCl and extracted with chloroform. The chloroform layer was washed with water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from methanol to give 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylic acid (0.443 g, 85%) as pale red prisms.

mp: 198 - 200 °C

Elementary Analysis for $C_{18}H_{19}NO_6$

Calc.: C, 63.86; H, 5.36; N, 3.92

Found: C, 64.09; H, 5.44; N, 3.85

Examples 82 - 85

Compounds listed in Table 5 were obtained by the same manner as in Example 81.

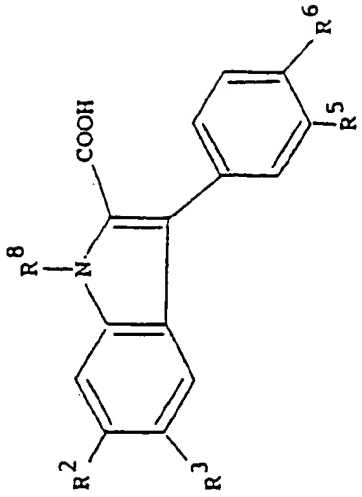


Table 5

No. of Examples	R^2	R^3	R^5	R^6	R^8	Yield (%)	MP(°C)	Solvent for recrystallization
82	CH_3O	CH_3O	H	CH_3O	H	94	198 - 200	ether - isopropyl ether
83	CH_3O	CH_3O	$-OCH_2O-$		H	87	227 - 229	acetone - methanol
84	$-O(CH_2)_2O-$		CH_3O	CH_3O	H	85	235 - 236	acetone - methanol
85	CH_3O	CH_3O	CH_3O	CH_3O	C_2H_5	91	189 - 190	acetone

Example 86

Oxalyl chloride (0.1 ml) was added to a solution of 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylic acid (0.357 g) and N,N-dimethylformamide (1 drop) in tetrahydrofuran (10 ml) and stirred for 30 minutes at room temperature. The resultant was concentrated under reduced pressure. The residue was

dissolved in tetrahydrofuran (5 ml). On the other hand, oily sodium hydride (60%, 0.133 g) was added to a solution of diethylaminophosphonate (0.92 g) in tetrahydrofuran (5 ml) with ice-cooling and stirred for 15 minutes at the same temperature. To the resultant mixture was added the above-mentioned tetrahydrofuran solution with ice-cooling. The reaction mixture was stirred for 30 minutes with ice-cooling, poured into water and extracted with ethyl acetate. The ethyl acetate layer was successively washed with sodium hydrogen carbonate saturated aqueous solution, 2N-HCl and water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from ethyl acetate to give N-diethoxyphosphoryl-5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxamide (0.056 g, 11%) as pale yellow prisms.
mp: 217 - 219 °C

Elementary Analysis for $C_{23}H_{29}N_2O_8P \cdot H_2O$

Calc.: C, 54.12; H, 6.12; N, 5.49

Found: C, 54.12; H, 5.99; N, 5.49

Example 87

Oxalyl chloride (0.06 ml) was added to a solution of 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylic acid (0.2 g) and N,N-dimethylformamide (1 drop) in tetrahydrofuran (10 ml) and stirred for 30 minutes at room temperature. The resulting solution was concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (5 ml). The tetrahydrofuran solution was added to a solution of diethyl 4-aminobenzylphosphonate (0.204 g) and triethylamine (0.09 ml) in tetrahydrofuran (10 ml). The reaction mixture was stirred for 2 hours at room temperature, poured into water and extracted with chloroform. The chloroform layer was successively washed with water, sodium hydrogen carbonate saturated aqueous solution, water, 2N-HCl and water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from ethyl acetate to give N-[4-(diethoxyphosphorylmethyl)-phenyl-5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxamide (0.283 g, 87%) as pale yellow prisms.
mp: 213 - 215 °C

Elementary Analysis for $C_{30}H_{35}N_2O_8P \cdot 1/2H_2O$

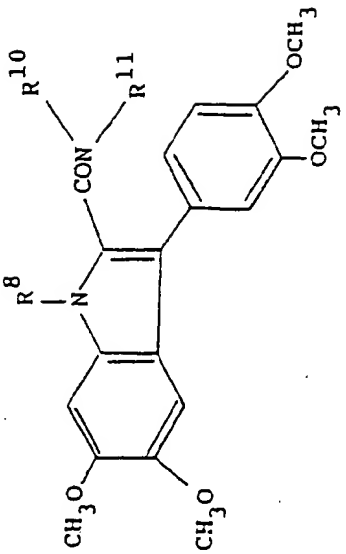
Calc.: C, 60.91; H, 6.13; N, 4.74

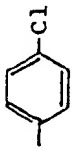
Found: C, 61.07; H, 6.17; N, 4.45

Examples 88 - 90

Compounds listed in Table 6 were obtained by the same manner as in Example 87.

Table 6



No. of Example	R^8	R^{10}	R^{11}	Yield (%)	MP(°C)	Solvent for recrystallisation
88	H	H		70	191 - 192	ethyl acetate
89	H	H	$-(CH_2)_2P(O)(OC_2H_5)_2$	60	176 - 177	ethyl acetate
90	Et	H		65	195 - 196	ether

Example 91

A solution of boron tribromide (BBr_3) (0.18 ml) in dichloromethane (0.36 ml) was dropwise added to a solution of methyl 3-(4-methoxyphenyl)-5,6-dimethylindole-2-carboxylate (0.3 g) in dichloromethane (10 ml)

at 0 °C. The reaction mixture was stirred for 2 hours at the same temperature, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from acetone to give methyl 3-(4-hydroxyphenyl)-5,6-dimethylindole-2-carboxylate (0.127 g, 44%) as colorless needles.
mp: 247 - 248 °C

Elementary Analysis for $C_{18}H_{17}NO_3$

Calc.: C, 73.20; H, 5.80; N, 4.74

Found: C, 72.98; H, 5.91; N, 4.68

Examples 92 - 98

Compounds listed in Table 7 were obtained by the same manner as in Example 91.

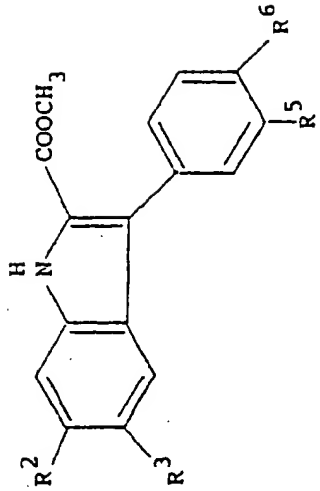


Table 7

No. of Examples	Starting Compound (No. of Examples)	R^2	R^3	R^5	R^6	Yield (%)	MP(°C)	Solvent for recrystallization
92	26	H	OH	CH_3	CH_3	45	192-193	acetone
93	15	CH_3	CH_3	OH	OH	40	212-214	acetone
94	1	OH	OH	CH_3	CH_3	63	179-180	acetone
95	3	OH	OH	H	OH	89	256-257	acetone
96	2	OH	OH	OH	OH	85	288-290	ether
97	14	$-O(CH_2)_2O-$		OH	OH	80	257-258	acetone - ether
98	24	$-O(CH_2)_2O-$		H	OH	80	262-263	ether

Example 99

Potassium carbonate (0.701 g) and ethyl iodide (0.42 ml) were added to a solution of methyl 5,6-dihydroxy-3-(3,4-dihydroxyphenyl)indole-2-carboxylate (0.2 g) in N,N-dimethylformamide (10 ml). The mix-

ture was stirred at room temperature overnight, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The residue was subjected to a silica gel column chromatography, eluting with ethyl acetate-hexane (1:4, v/v) to give methyl 5,6-diethoxy-3-(3,4-diethoxyphenyl)indole-2-carboxylate.

Recrystallization from ether-isopropylether gave colorless prisms (0.131 g, 48%).
mp: 134 - 135 °C

Elementary Analysis for $C_{24}H_{29}NO_6$

Calc.: C, 67.43; H, 6.84; N, 3.28

Found: C, 67.20; H, 7.01; N, 3.10

Examples 100 - 104

Compounds listed in Table 8 were obtained by the same manner as in Example 99.

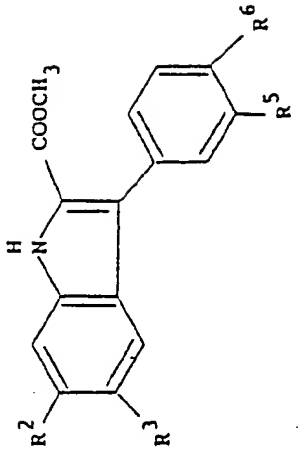


Table 8

No. of Examples	Starting Compound (No. of Examples)	R^2	R^3	R^5	R^6	Yield (%)	MP(°C)	Solvent for recrystallization
100	95	OC_2H_5	OC_2H_5	H	OC_2H_5	36	138-139	isopropyl ether - hexane
101	97	$-O(CH_2)_2O-$		OC_2H_5	OC_2H_5	51	241-242	acetone
102	97	$-O(CH_2)_2O-$		$OCH(CH_3)_2$	$OCH(CH_3)_2$	17	222-223	methanol
103	98	$-O(CH_2)_2O-$		H	OC_2H_5	59	232-233	acetone-ether
104	98	$-O(CH_2)_2O-$		H	$OCH(CH_3)_2$	53	250-252	acetone

Example 105

Potassium carbonate (0.139 g) and ethyl iodide (0.13 ml) were added to a solution of 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylic acid (0.3 g) in N,N-dimethylformamide (5 ml). The mixture was

stirred for 3 hours at room temperature, poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from ethanol to give ethyl 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)-indole-2-carboxylate (0.272 g, 84%) as pale red prisms.
mp: 171 - 172 °C

Elementary Analysis for $C_{21}H_{23}NO_6$

Calc.: C, 65.44; H, 6.01; N, 3.63

Found: C, 65.54; H, 6.10; N, 3.62

Examples 106 - 110

Compounds listed in Table 9 were obtained by the same manner as in Example 105.

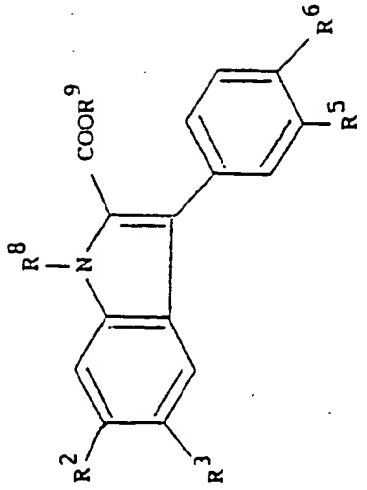


Table 9

No. of Examples	R^2	R^3	R^5	R^6	R^8	R^9	Yield (%)	MP(°C)	Solvent for recrystallization
106	CH_3O	CH_3O	CH_3O	CH_3O	H	$(CH_3)_2CH$	81	147-148	ether
107	$-O(CH_2)_2O-$		CH_3O	CH_3O	H	C_2H_5	79	213-214	acetone-ethanol
108	$-O(CH_2)_2O-$		CH_3O	CH_3O	H	$(CH_3)_2CH$	71	190-191	ether
109	CH_3O	CH_3O	CH_3O	CH_3O	C_2H_5	C_2H_5	83	125-126	methanol
110	CH_3O	CH_3O	CH_3O	CH_3O	C_2H_5	$(CH_3)_2CH$	80	124-125	methanol

Example 111

N,N-Dimethylformamide (3 drops) and oxalyl chloride (0.59 ml) were added to a solution of 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylic acid (2.0 g) in tetrahydrofuran (50 ml). The mixture was stirred for an hour at room temperature and concentrated under reduced pressure. The residue was dissolved in benzene (20 ml). This benzene solution was added to a solution of tert-butanol (0.79 ml) and N,N-dimethylaniline (0.85 ml) in benzene (30 ml), followed by stirring overnight at room temperature. The

mixture was successively washed with water, sodium hydrogen carbonate saturated aqueous solution and water, dried ($MgSO_4$) and concentrated. The precipitated crystals were collected by filtration and recrystallized from acetone to give tert-butyl 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylate (1.61 g, 70%) as colorless prisms.

mp: 185 - 186 °C

Elementary Analysis for $C_{23}H_{27}NO_6$

Calc.: C, 66.81; H, 6.58; N, 3.39

Found: C, 66.96; H, 6.67; N, 3.40

[Study on bone resorption inhibition]

Bone resorption inhibiroty activity was determined according to the method of Raisz [Journal of Clinical Investigation (J. Clin. Invest.) 44, 103-116 (1965)].

Thus, a Sprague-Dawley rat at day 19 of pregnancy was subcutaneously dosed with 50 μCi of ^{45}Ca (a radioisotope of calcium, in $CaCl_2$). On the next day, the animal was laparotomized and the fetuses were removed aseptically. The right and left humeri (radii and ulnae) of each rat fetus were dissected from the body under the dissection microscope. The connective tissue and cartrilages were removed as far as possible to prepare bone culture specimens. Each piece of bone was incubated in 0.6 ml of BGJ_b medium (Fitton-Jackson modification [the tradename owned by GIBCO Laboratories, U.S.A.]) containing 2 mg/ml of bovine serum albumin at 37 °C for 24 hours. Then, incubation was carried out for additional two days in the above-mentioned medium. The radioactivities of ^{45}Ca in the culture medium and bone were determined and the ratio (%) of ^{45}Ca released from the bone to the medium was calculated according to the following formula.

$$A = \frac{B}{B + C} \times 100$$

A = ratio (%) of ^{45}Ca released from the bone to the medium

B = ^{45}Ca count in the medium

C = ^{45}Ca count in the bone

The bones from the fetuses of the same litter were similarly incubated without addition of the test compound for two days and served as controls.

The values for 5 bones per group were expressed in mean. The ratio (%) of this value for the treatment group to the control value was determined. The results are shown in Table 10.

Table 10

Compounds Exmple No.	^{45}Ca discharge (% to control) 10μg/ml (conc. of specimen)	1μg/ml (conc. of specimen)
1	52***	
3	44***	54***
7	54**	75*
9	56**	
10	52**	
11	53***	41***
20	56***	
24	58***	55**
26	59*	
28	46***	
45	59***	69**
53	77***	
77	52***	51**
78	57*	37***
84	59***	
89	74*	
97	46***	60**
98	47***	
100	47***	71*

*** $p<0.001$, ** $p<0.01$ * $p<0.05$

As is apparent from Table 10, the compounds (I) possess excellent activity for inhibiting bone resorption. Accordingly, the compound (I) can be used as an inhibitor for bone resorption for mammals (e.g., mouse, rat, rabbit, dog, cat, cow, pig and human being).

The compounds of the invention can be administered to human being through any of oral or parenteral route.

Compositions for oral administration may be solid or liquid forms, specifically tablets (including sugar coated tablets and film coated tablets), pills, granules, powders, capsules (including soft capsules), syrups, emulsions and suspensions. Such compositions will contain conventional carriers or excipients and can be prepared by known methods. Examples of the carriers or excipients for tablets are lactose, starch, sucrose and magnesium stearate.

Compositions for parenteral administration are e.g., injections and suppositories, the former of which includes subcutaneous, intracutaneous, intramuscular or like injections. Such injections can be prepared by

suspending or emulsifying the compound (I) in or with sterile aqueous or oily liquids which are usually employed in injections, in accordance with the methods known in the art. Examples of the aqueous liquids for injections are physiological saline and isotonic solution, which may be used together with a suitable suspending agent such as sodium carboxy methylcellulose or a nonionic surfactant upon circumstances. Examples of the oily liquids are sesame oil and soybean oil, which may be used together with a solubilizing agent such as benzyl benzoate or benzyl alcohol. The injections thus prepared are usually put into ampoules.

The oral dosage of the compound (I) or a salt thereof when used as therapeutic agent for an inhibitor for bone resorption is 1 to 500 mg/day, preferably 10 to 150 mg/day for an adult.

Preparation Example 1

Tablets

Components of a tablet	
(1) Compound of Example 2	50.0mg
(2) Cornstarch	30.0mg
(3) Lactose	113.4mg
(4) Hydroxypropyl cellulose	6.0mg
(5) Water	(0.03ml)
(6) Magnesium stearate	0.6mg
Total	200.0mg

The components (1), (2), (3) and (4) were mixed. After adding water, the mixture was kneaded, dried under vacuum for 16 hours at 40 °C and grounded in a mortar. The resultant was sieved through a 16-mesh sieve to give granules. The component (6) was added to the granules and mixed. The resulting mixture was made to tablets of 200mg per tablet, using a rotary-type tablet machine (Kikusui Seisakusho in Japan).

Preparation Example 2

(1) Compound of Example 14	50.0mg
(2) Cornstarch	30.0mg
(3) Lactose	113.4mg
(4) Hydroxypropyl cellulose	6.0mg
(5) Water	(0.03ml)
(6) Magnesium stearate	0.6mg
(7) Cellulose acetate phthalate	10.0mg
(8) Acetone	(0.2ml)
Total	210.0mg

From the components (1), (2), (3), (4), (5) and (6), tablets were prepared by the same method as in Preparation Example 1. These tablets were film-coated by use of a solution of the component (7) in acetone in a bar coater (Freunt Co., Ltd.) to give entric coated tablets of 210mg per tablet.

Preparation Example 3

Component of a capsule	
(1) Compound of Example 45	30.0mg
(2) Cornstarch	40.0mg
(3) Lactose	74.0mg
(4) Hydroxypropyl cellulose	6.0mg
(5) Water	(0.02ml)
Total	150.0mg

The components (1), (2), (3) and (4) were mixed, to which water was added. The mixture was kneaded, dried under vacuum for 16 hours at 40° C and grounded in a mortar. The resultant was sieved through a 16-mesh sieve to give granules. The granules were packed in No. 3 gelatin capsules with a capsule packing machine (Zanassi Italy) to obtain capsules.

Preparation Example 4

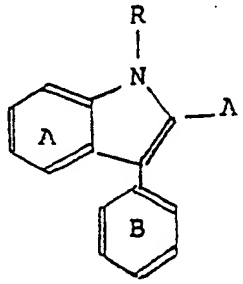
Component of a capsule	
(1) Compound of Example 48	5.0mg
(2) Sodium salicylate	50.0mg
(3) Sodium chloride	180.0mg
(4) Sodium metabisulfite	20.0mg
(5) Methylparaben	36.0mg
(6) Propylparaben	4.0mg
(7) Distilled water for injection	(2.0ml)
Total	295.0mg

The components (2), (3), (4), (5) and (6) were dissolved in about one half of the above-mentioned volume of distilled water under stirring at 80°C. The solution thus obtained was cooled to 40°C, to which the compound of the present invention was dissolved. The remaining distilled water was added to the solution so that a final volume can be obtained. The resultant was sterilized through an appropriate filter paper, to give the injection.

The compounds of the present invention possess excellent activity for inhibiting bone resorption and improve bone metabolism by directly working on bones. Accordingly, the compounds of the present invention can be used as a therapeutic agent for osteoporosis.

Claims

1. Pharmaceutical composition which comprises a therapeutic effective amount of an indole derivative of the formula (I):



(I)

wherein each ring of A and B is optionally substituted, R is a hydrogen atom, a lower alkyl group or an acyl group, and A is a hydroxymethyl group or an esterified or amidated carboxyl group;
or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier, diluent or excipient.

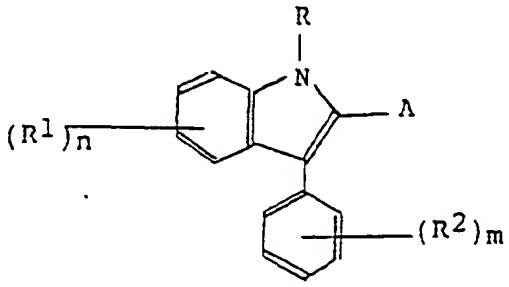
2. Composition of claim 1 in which the ring A and/or B in the formula (I) are not substituted or substituted by one to four of an optionally substituted hydroxyl or alkyl group.

3. Composition of claim 1 in which the ring A in the formula (I) is substituted by two methoxy groups or is combined with an alkylenedioxy to form a ring and the ring B is substituted by two or three methoxy or ethoxy groups or combined with an alkylenedioxy to form a ring.

4. Composition of claim 1 in which the indole derivative (I) is methyl 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylate, 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)-2-hydroxymethylindole, methyl 3-(3,4-dimethoxyphenyl)-5,6-ethylenedioxyindole-2-carboxylate, 3-(3,4-dimethoxyphenyl)-5,6-ethylenedioxy-2-hydroxymethylindole or methyl 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)-1-ethylindole-2-carboxylate.

5. Pharmaceutical composition according to claims 1 to 4 for inhibiting bone resorption especially for the treatment of osteoporosis.

6. An indole derivative of the formula (I'):



(I')

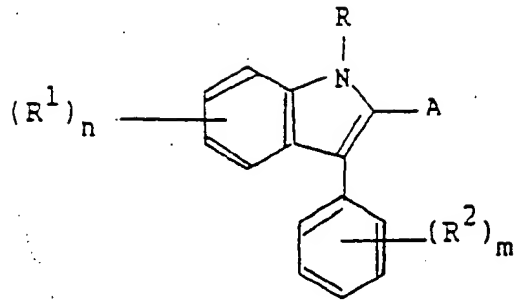
wherein R^1 and R^2 each is, the same or different, an optionally substituted hydroxyl group or an optionally substituted alkyl group, or two of each of R^1 and R^2 may be a bivalent hydrocarbon residue or alkylenedioxy group to form a ring together with the ring to which they are attached, R is a hydrogen atom, a lower alkyl group or an acyl group, A is a hydroxymethyl group or an esterified or amidated carboxylic group and n and m each is an integer of two to four;
or its salt.

7. The compound of claim 6 in which R is a hydrogen atom or a lower alkyl, and A is a carboxyl group optionally substituted by a lower alkyl, a carbamoyl group optionally substituted by a lower alkyl.

8. The compound of claim 7 in which n is 2 or 3 and R^1 is a lower alkyl group or a hydroxyl group substituted by a lower alkyl, or two of R^1 are an alkylenedioxy to form a ring together with the ring to which they are attached; m is 2, 3 or 4 and R^2 is a hydroxyl group substituted by a lower alkyl, a lower alkyl group or two of R^2 are an alkylenedioxy to form a ring together with the ring to which they are attached.

9. The compound of claim 7 which is methyl 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)indole-2-carboxylate, 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)-2-hydroxymethylindole, methyl 3-(3,4-dimethoxyphenyl)-5,6-ethylene-dioxyindole-2-carboxylate, 3-(3,4-dimethoxyphenyl)-5,6-ethylenedioxy-2-hydroxymethylindole or methyl 5,6-dimethoxy-3-(3,4-dimethoxyphenyl)-1-ethylindole-2-carboxylate.

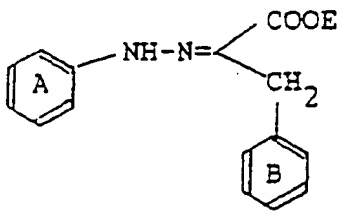
10. A process for preparing an indole derivative of the formula (I'):



(I')

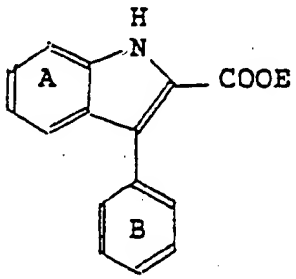
wherein R^1 and R^2 each is, the same or different, an optionally substituted hydroxyl group or an optionally substituted alkyl group, or two of each of R^1 and R^2 may be a bivalent hydrocarbon residue or alkylenedioxy group to form a ring together with the ring to which they are attached, R is a hydrogen atom, a lower alkyl group or an acyl group, A is a hydroxymethyl group or an esterified or amidated carboxylic group and n and m each is an integer of two to four;
or its salt,
which comprises:

A) heating a compound of the formula (II):



(II)

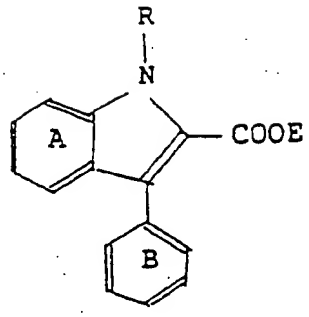
to obtain a compound of the formula (I-1):



(I-1)

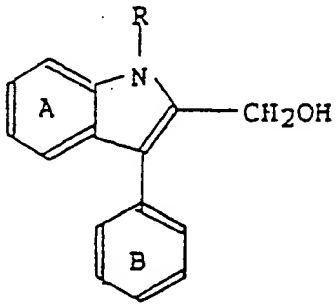
wherein E is an ester residue for the esterified carboxyl, the ring A and ring B have the substituents $(R^1)_n$ and $(R^2)_m$ as in the formula (I'), respectively;

B) reacting a compound of the formula (I-1) with a compound of the formula R-X wherein R is the same meaning as in the formula (I') and X is a leaving group to obtain a compound of the formula (I-2):



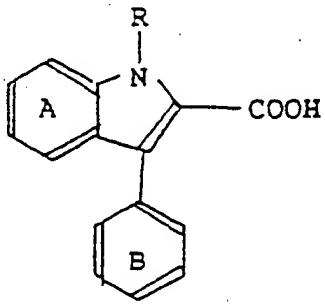
(I-2)

wherein the symbols are as defined above;
C) reducing a compound of the formula (I-2) to obtain a compound of the formula (I-3)



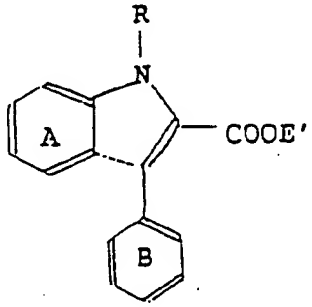
(I-3)

wherein the symbols are as defined above;
D) hydrolyzing a compound of the formula (I-1) or (I-2) to obtain a compound of the formula (I-4):



(I-4)

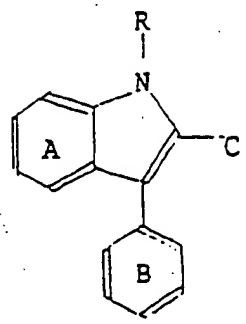
wherein the symbols are as defined above;
E) esterfying a compound of the formula (I-4) to obtain a compound of the formula (I-5):



(I-5)

wherein E^1 has the same meanings as defined for E and the other symbols are as defined above;

F) amidating a compound of the formula (I-4) to obtain a compound of the formula (I-6):



(I-6)

wherein C is an amidated carboxyl group and the other symbols are as defined above;
G) eliminating a substituent in the substituted hydroxyl group of a compound of the formula (I') to obtain a compound of the formula (I') wherein R^1 and/or R^2 are hydroxyl group; or
H) converting a compound of the formula (I') wherein R^1 and/or R^2 are hydroxyl group into the corresponding compound wherein R^1 and/or R^2 are a substituted hydroxyl group through alkylation, aralkylation or acylation; and if necessary
I) converting a compound of the formula (I') into the corresponding salt.

11. Use of a compound of the formula (I) according to any of claims 6 to 9 for the preparation of a pharmaceutical composition for inhibiting bone resorption.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 91 10 4746

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 068 563 (THE PROCTER & GAMBLE COMPANY) * page 21, line 6 - line 7 * *	6,11	C 07 D 209/42 A 61 K 31/40 C 07 D 209/12 C 07 D 209/60 C 07 D 209/70 C 07 D 405/04 C 07 D 491/04 C 07 F 9/572
A	US-A-4 185 108 (C.M. SAMOUR) * column 8 - column 10; claims 1,2,8 * *	6,11	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	13 February 92	FINK D.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

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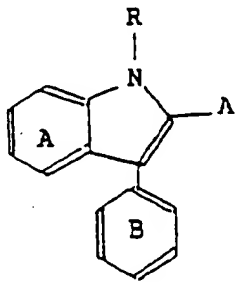
(54) Indole derivatives, their production and use.

(57) An agent for inhibiting bone resorption comprising an indole derivative of the formula (I):



(I)

wherein each ring of A and B is optionally substituted, R is a hydrogen atom, a lower alkyl group or an acyl group, and A is a hydroxymethyl group or an esterified or amidated carboxyl group; or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier, diluent or excipient.

EP 0 449 196 A3